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Morphology Rounds at the University of Rochester:

Disorders That Resemble Lymphomas

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INTRODUCTION

Each physician sees the patient in the light of prior experience and, as a result, a bias in the interpretation of clinical and laboratory clues may influence expectations and even management of the clinical course. For the expert in infectious diseases, organomegaly can evoke images of bacterial, viral, or fungal infiltration or inflammation, while the gastroenterologist may think first of portal hypertension and the immunologist of non-infectious granulomatous disease. The hematologist or oncologist would require no encouragement to see lymphomatous infiltration as the explanation of hepatosplenomegaly, especially with concomitant lymphadenopathy and cytopenias. It is not uncommon for the clinician to be faced with a patient in whom the presenting symptoms suggest a malignant lymphoma but pathologic diagnosis shows a benign lymphoproliferative disorder or a serious but non-malignant process. The proper identification and classification of these disorders requires review by an experienced pathologist.

In this series of three cases, we present patients with lymphadenopathy and systemic manifestations that were highly suggestive of lymphoma, but which, after appropriate study, represented examples of strikingly different pathologic processes. Although there were some clinical clues present, these patients required pathologic examination of the lymph node in order for the distinction to be made.

CASE 1. CASTLEMAN'S DISEASE

Case Description

The patient is a 57-year-old white male who was in good health until 2 weeks prior to admission when palpable splenomegaly was found during a routine physical examination. He had lost 10 pounds in weight over the preceeding 3 months and subsequently developed low-grade fevers and night sweats, then left upper quadrant abdominal pain 5 days prior to admission. On physical examination, temperature was 38.5°C, pulse 100/min, and blood pressure 110/70 mm Hg. There was no cervical lymphadenopathy but a 2-cm left anterior axillary and a 1.5-cm left inguinal lymph node were palpable. Lungs were clear, heart rhythm was regular, a soft systolic ejection murmur was present, and the abdomen was soft with active bowel sounds. The spleen was tender to palpation and was enlarged to 15 cm below the left costal margin and the liver edge was palpable 4 cm below the right costal margin in the midclavicular line. There was no dependent edema.

Laboratory data included a white blood cell count of 7,600/μL, hematocrit 38% and platelet count 274,000/μL, and the peripheral blood smear showed neutrophils with toxic granulation. The total serum globulin was elevated at 5.1 g/dl and serum protein electrophoresis showed a polyclonal gammopathy. Serum aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and alkaline phosphatase levels were normal. Chest X-ray was normal and computerized tomography scan of the abdomen confirmed splenomegaly but not hepatomegaly and there was no lymphadenopathy. A bone marrow examination showed eosinophilia (5%) and plasmacytosis (10%). Biopsy of the axillary lymph node showed angiofollicular hyperplasia (Fig. 1A–C), consistent with Castleman's Disease [1]. His systemic symptoms improved transiently after initiation of steroid therapy (Prednisone 100 mg/d) and he was discharged. However, symptoms of fever, sweats, and left upper quadrant discomfort recurred when the steroids were tapered. Cytoxan (1.0 g) and Vincristine (1.0 mg) were administered intravenously, but he was readmitted 2

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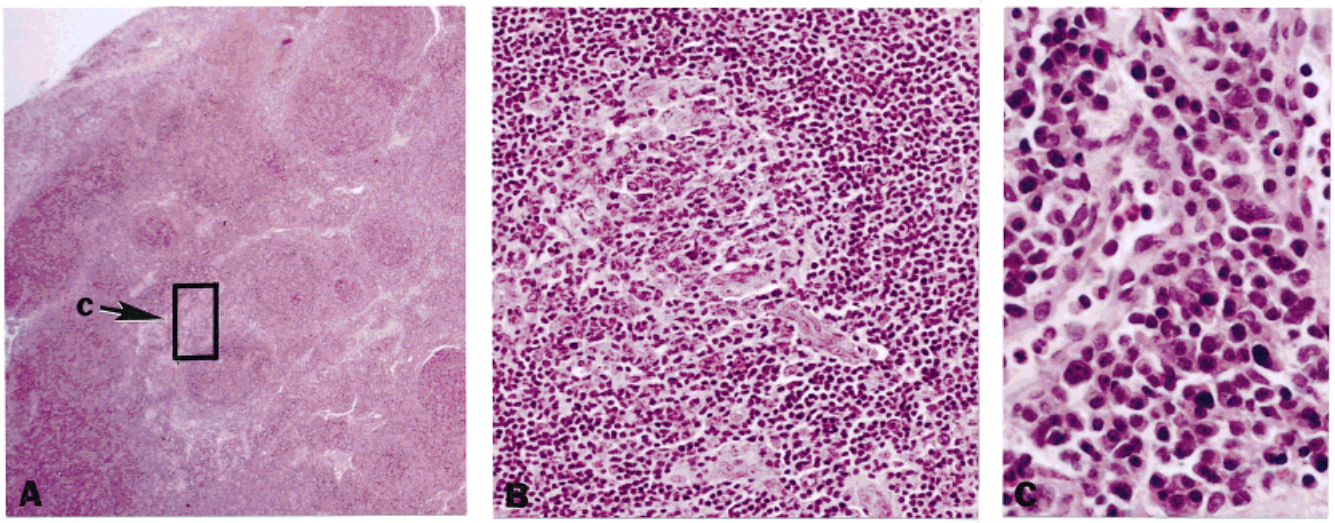
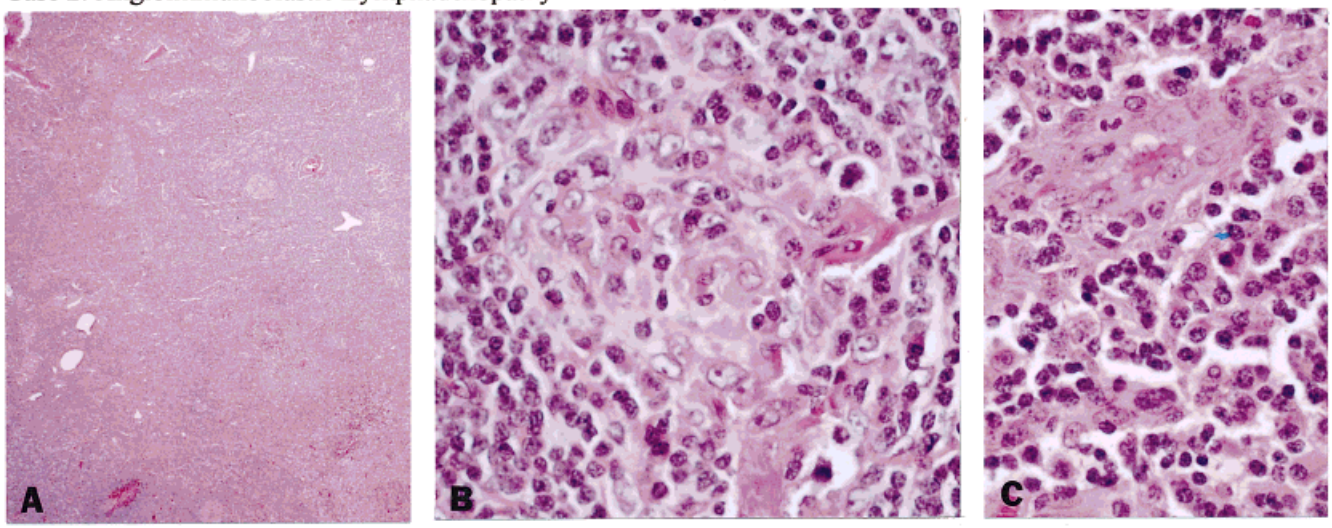
Case 1: Castleman's Disease



Case 2: Angioimmunoblastic Lymphadenopathy



Case 3: Sarcoidosis

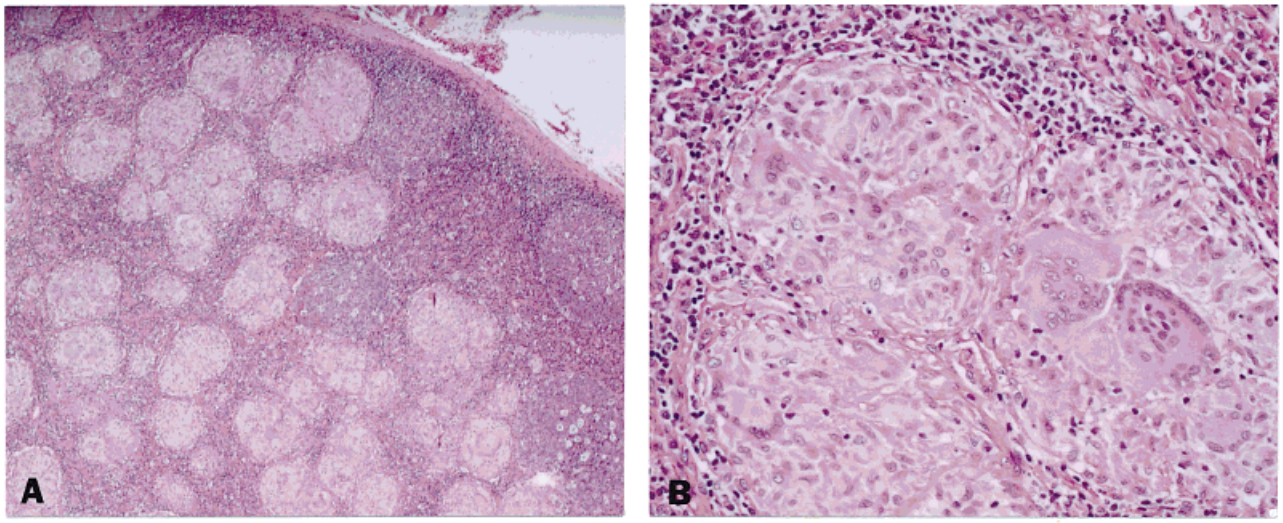


Fig. 1. Castleman's Disease. A: Lymph node biopsy (hematoxylin and eosin, ×40) showing preservation of architecture, although margins of germinal centers are indistinct. B: Lymph node (×200). Ill-defined germinal center with loss of mantle zone, decreased cellularity, and prominent vascularity. C: Lymph node (×400). High-power view of area marked by arrow (labelled C) in A; infiltration of interfollicular region by sheets of plasma cells.
Fig. 2. Angioimmunoblastic lymphadenopathy with dysproteinemia. A: Right axillary lymph node (×40) showing effacement of normal architecture. B: Lymph node (×400). Partially obliterated germinal center with penetration by thick-walled vessels. C: Lymph node (×400) showing prominent vessel with hyperplastic endothelial lining; polymorphous infiltrate of lymphocytes, plasma cells and immunoblasts.
Fig. 3. Sarcoidosis. A: Left cervical lymph node (×40) shows replacement of architecture by well-circumscribed non-caseating granulomas. B: Lymph node (×200). Granuloma with Langhans' and foreign body type multinucleated giant cells.

weeks later with worsening abdominal pain and fever, dyspnea, and generalized aches. The platelet count dropped over the next several days to a nadir of 31,000/μL and an urgent splenectomy was performed. Microscopic findings included striking architectural effacement and lymphoid depletion with no identifiable white pulp, and diffuse infiltration with plasma cells, lymphocytes, and immunoblasts. There was no clear-cut predominance of kappa or lambda light chains on immunohistochemical study. Post-operative course was marked by recurrent fever, persistent severe abdominal pain, and hypoxemia with a high alveolar:arterial gradient. Progressive multiorgan failure developed over the following 2 weeks and the patient expired approximately 3 months following the initial diagnosis. Post-mortem examination was not performed.

Comment

Angiofollicular lymph node hyperplasia was first described by Castleman et al. in 1956 [1] as a localized mediastinal process characterized pathologically by small hyalinized follicle centers with radially penetrating vessels and prominent interfollicular vascular proliferation. Subsequently, this ''hyaline-vascular type'' was distinguished from a ''plasma cell type,'' the latter characterized by sheets of plasma cells intervening between the hyperplastic germinal centers. The hyaline-vascular variant is more common, accounting for 91% of cases [2] and is characterized by a benign clinical course. Patients are usually asymptomatic and often present with a mediastinal mass that is incidentally detected by chest roentgenography.

More recently, a distinct lymphoproliferative disorder with similar histologic features but more generalized involvement has been described as multicentric angiofollicular lymphoid hyperplasia or multicentric Castleman's Disease [3–5]. This clinicopathologic entity has histologic features of the plasma cell type of Castleman's Disease and involves multiple peripheral nodes as well as the bone marrow, liver, spleen, kidney, and nervous system. Characteristic pathologic features include preservation of lymph node architecture, but with expanded, hypervascularized, often ill-defined germinal centers and interfollicular plasmacytosis. The case presented here showed all of these features and plasma cell infiltration was prominent.

The clinical features of multicentric (generalized) Castleman's Disease are variable and the onset of symptoms can be abrupt or insidious. When the presentation is relatively acute, as was the case in our patient, it resembles that which may occur in patients with a high-grade lymphoma, including lymphadenopathy, organomegaly, and systemic symptoms of fever, night sweats, weight loss, fatigue, and weakness. The laboratory features show only a non-specific anemia and an increased erythrocyte sedimentation rate, but thrombocytopenia is relatively common (60% of cases) and, as in our case, can be quite dramatic. The clinical diagnosis is usually lymphoma and the diagnosis of Castleman's Disease requires lymph node biopsy. The clinical course is quite variable, ranging from a rapidly progressive illness with a lethal outcome to a more prolonged, indolent course that is more typically associated with localized Castleman's Disease. Median survival is 29 months with 13% living 10 years or longer [5].

The etiology of Castleman's Disease is not known, although immuno-dysregulation involving interleukin-6 expression has been implicated, providing a foundation for the use of antibody against interleukin-6 therapeutically [6]. Steroids as well as cytotoxic chemotherapy have been used with limited success in Castleman's Disease, although there have been anecdotal reports of durable remissions following these treatments. Our patient exemplifies the rapidly fatal course with multiorgan failure that can characterize this disorder. Although studies have failed to show Castleman's Disease to be clonal in nature, its clinical behavior can nevertheless be quite aggressive.

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CASE 2. ANGIOIMMUNOBLASTIC LYMPHADENOPATHY WITH DYSPROTEINEMIA

Case Description

The patient, a 27-year-old white female infected with the human immunodeficiency virus (HIV), was seen in consultation for possible lymphoma. She had been HIV positive for the previous 8 years, having been infected through heterosexual exposure. Generalized lymphadenopathy had been noted for at least 6 months, and for 2 months she had experienced intermittent fever. The last T-helper cell count was 62/μL (normal 400–1,400 μL) 3 months earlier, but there was no history of opportunistic infection. Medications consisted of erythropoietin, ferrous sulfate, and monthly pentamidine. Physical examination revealed a thin, but well-appearing woman with generalized lymphadenopathy and hepatosplenomegaly, the spleen extending 4 cm below the left costal margin. The white blood cell count was 2,400/μL, with 30% neutrophils, 5% band forms, 52% lymphocytes, and 13% monocytes. The hematocrit was 22% and the platelet count 56,000/μL, and the direct Coomb's test was negative. Serum lactate dehydrogenase was 183 IU/L (normal 100–190 IU/L).

Bone marrow biopsy revealed a hypercellular marrow with all cell lines present and maturing normally. A single lymphohistiocytic aggregate was seen. A right axillary lymph node biopsy showed findings characteristic of angioimmunoblastic lymphadenopathy with dysproteinemia (Fig. 2A–C); gene rearrangement studies showed a T-cell clone and serum protein electrophoresis displayed a polyclonal gammopathy. Over the next few months, the patient noted intermittent fevers accompanied by night sweat and weight loss, and the spleen gradually enlarged and became increasingly painful. Elective splenectomy was performed, and the findings were similar to those noted in the biopsied lymph node.

Comments

Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) is a rare lymphoproliferative disorder first described independently by several authors in the 1970s. AILD affects men and women equally at a median age of 60 years. The presentation usually resembles that of a high-grade lymphoma, with generalized lymphadenopathy, hepatosplenomegaly, and systemic symptoms of fever, malaise, night sweats, and weight loss. Laboratory findings often include a polyclonal gammopathy, leukocytosis, and lymphopenia, and immune hemolysis and thrombocytopenia are not infrequent. A clinical clue to the diagnosis of AILD is that nearly one-third of the patients have been exposed to specific medications, vaccinations, or a viral infection, or that it occurs in association with an autoimmune disease such as systemic lupus erythematosus. Despite this caveat, the clinical diagnosis is usually lymphoma and lymph node biopsy is required to make the diagnosis of AILD. Histopathologic findings of the lymph nodes and spleen reflect a dysregulated immune system, with infiltration by immunoreactive cells (immunoblasts, plasma cells, lymphocytes, eosinophils, and histiocytes), which may efface the nodal architecture and germinal centers. There is prominent arborization of post-capillary venules and a characteristic amorphous proteinaceous material is pervasive in the background. The predominant infiltrating cells in the lymph nodes are T-cells, which presumably stimulate B-cells to proliferate in a polyclonal manner. Patients often die from infection by either normal pathogens or opportunistic organisms, and median survival is 18–36 months, with approximately 25% of patients following a relatively benign course [1].

Evidence of clonal proliferation is often seen as exemplified by the clonal gene rearrangement in our patient. This finding does not always signify the presence of lymphoma, leading some authors to suggest that AILD is an oligoclonal lymphoproliferative disorder in which many of the clones may spontaneously regress [1]. However, 5–20% of patients develop malignant lymphoma, usually of the large cell immunoblastic type; cell markers are often consistent with peripheral T-cell lymphoma. A broad spectrum of chromosomal rearrangements have been reported, including trisomy 3, trisomy 5, and additional X-chromosome, but no consistent non-random marker has been identified [2].

Although corticosteroids can induce dramatic improvement in symptoms, they appear to cause a higher incidence of infectious complications. The addition of an alkylating agent has been associated with both an improvement and worsening of the outcome in different series. When lymphoma is present, intensive combination chemotherapy may induce complete remission rates of up to 60%, although durable responses are uncommon [3]. Other treatments that have been tried with varying success include alpha interferon, cyclosporine A, and autologous bone marrow transplantation.

There is considerable similarity in the clinical appearance of AILD and the non-specific lymphadenopathy often seen in patients who are infected with HIV, making the clinicopathologic diagnosis particularly challenging in this setting [4]. Distinquishing features of AILD in HIV-positive individuals include the presence of typical

immunoblasts, vascular arborization, and effacement of lymph node architecture.

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CASE 3. SARCOIDOSIS WITH LYMPHADENOPATHY AND SPLENOMEGALY

Case Description

The patient is a 24-year-old African-American male with a past medical history of childhood asthma who was well prior to the occurrence of an upper respiratory infection, night sweats, and a mild bleeding diathesis characterized by epistaxis, gingival oozing, and blood-streaked sputum. There was no history of fever, weight loss, anorexia, or major bleeding. There was no history of a prior bleeding disorder or bleeding in the family.

On physical examination, he was healthy-appearing and had normal vital signs. Petechiae and blood were present in the nose and mouth and there was generalized lymphadenopathy, with 2-cm nodes palpable in the anterior cervical chain, the right axilla, and in both inguinal areas. Lung exam was normal. Heart rate was regular but a soft systolic murmur was heard over the entire precordium. The liver edge was felt 2 cm below the right costal margin and the spleen 5 cm below the left costal margin.

Laboratory data revealed a hematocrit of 34%, mean red cell volume 69 μ^3, white blood cell count 2,600/μL, and platelet count 3,000/μL. White blood cell differential showed 52% neutrophils, 13% band forms, 18% lymphocytes, 16% monocytes, and 1% myelocytes. The Wright-stained peripheral blood showed normal neutrophil morphology, poikilocytosis, hypochromia, markedly decreased platelets, and a rare plasmacytoid lymphocyte. The monospot test was negative. The bone marrow showed expanded erythropoiesis, orderly granulopoiesis, increased megakaryocytes, 10–15% normal-appearing lymphocytes, and no increase in plasma cells.

The working diagnoses were immune thrombocytopenia, possibly secondary to lymphoma, possible post-viral syndrome, or HIV infection. The leukopenia was felt to be due to hypersplenism. There was no significant response of the bleeding or thrombocytopenia to intravenous immune globulin or to platelet transfusion. Following lymph node biopsy, he received intravenous methylprednisolone but continued to have oral and nasal bleeding, hematuria, and bleeding into the biopsy site. His platelet count remained between 3,000 and 17,000/μL. Splenectomy was performed 7 days after admission; the post-operative course was uncomplicated and there was resolution of thrombocytopenia, after which steroids were tapered and he was discharged.

Lymph node biopsy showed noncaseating granulomas consistent with sarcoidosis (Fig. 3A,B), but no evidence of lymphoma. The spleen contained visible small nodules and, histologically, the diagnosis of sarcoidosis was confirmed. He received no additional therapy for sarcoidosis and has not had a recurrence of adenopathy or thrombocytopenia.

Comments

Sarcoidosis is a systemic disease with variable clinical presentations. Most patients have some evidence of pulmonary involvement; however, many also have infiltration of other organs such as the skin, eyes, lymph nodes, liver, and nervous system [1]. The case presented here is notable for the absence of pulmonary involvement, the presence of marked immune thrombocytopenia, and significant lymphadenopathy and splenomegaly that suggested the presence of a lymphoproliferative disease.

Intrathoracic lymphadenopathy is present in 75–90% of patients with sarcoidosis, most commonly in the hilar or paratracheal regions, but peripheral adenopathy is also often present. Splenomegaly is clinically detectable in 5–10% of cases, but histologically proven granulomatous involvement is present in 50–60% of cases. Bone marrow involvement occurs in 15–40% of cases but is usually not associated with severe cytopenias [1]. Immune thrombocytopenia is rare and occurs in only 1–2% of cases [2–4].

The etiology of sarcoidosis is unknown. However, it is postulated that it is caused by an exaggerated immune response that leads to the formation of granulomas comprised of macrophages and T helper lymphocytes. The prevalence of sarcoidosis varies considerably throughout the world, and there does not appear to be a specific HLA association. Treatment usually includes glucocorticoids or other immunosuppressive drugs, and many cases remit spontaneously.

The patient described received intravenous gammaglobulin and methylprednisolone to treat his immune thrombocytopenia. However, it appeared that the splenectomy was the most helpful modality used. The patient did extremely well clinically and has not had a recurrence of his thrombocytopenia, lymphadenopathy, or other evi-

dence of sarcoidosis. Sarcoidosis should be considered in the differential diagnosis of patients with disseminated lymphadenopathy independent of the classic pulmonary manifestations.

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